Armed Forces College of Medicine

AFCM

Lecture Title

Hyperuricemia and gout

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INTENDED LEARNING OBJECTIVES (ILOs)

By the end of this lecture the student will be able to:

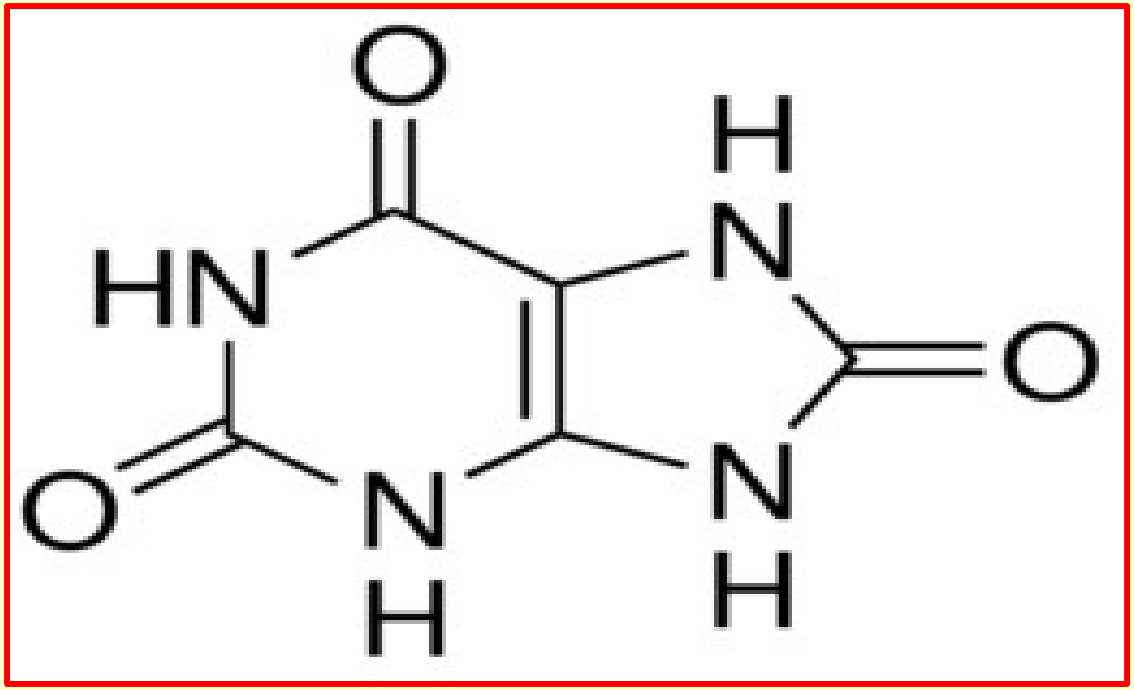
1. Illustrate steps of purine catabolism
2. Demonstrate causes of hyperuricemia
3. Interpret biochemical basis of gout and its treatment
4. Correlate purine metabolism with immune

Catabolism of Purine nucleotides

1-Dietary purine nucleotides are degraded to Uric Acid in intestinal mucosal cells.

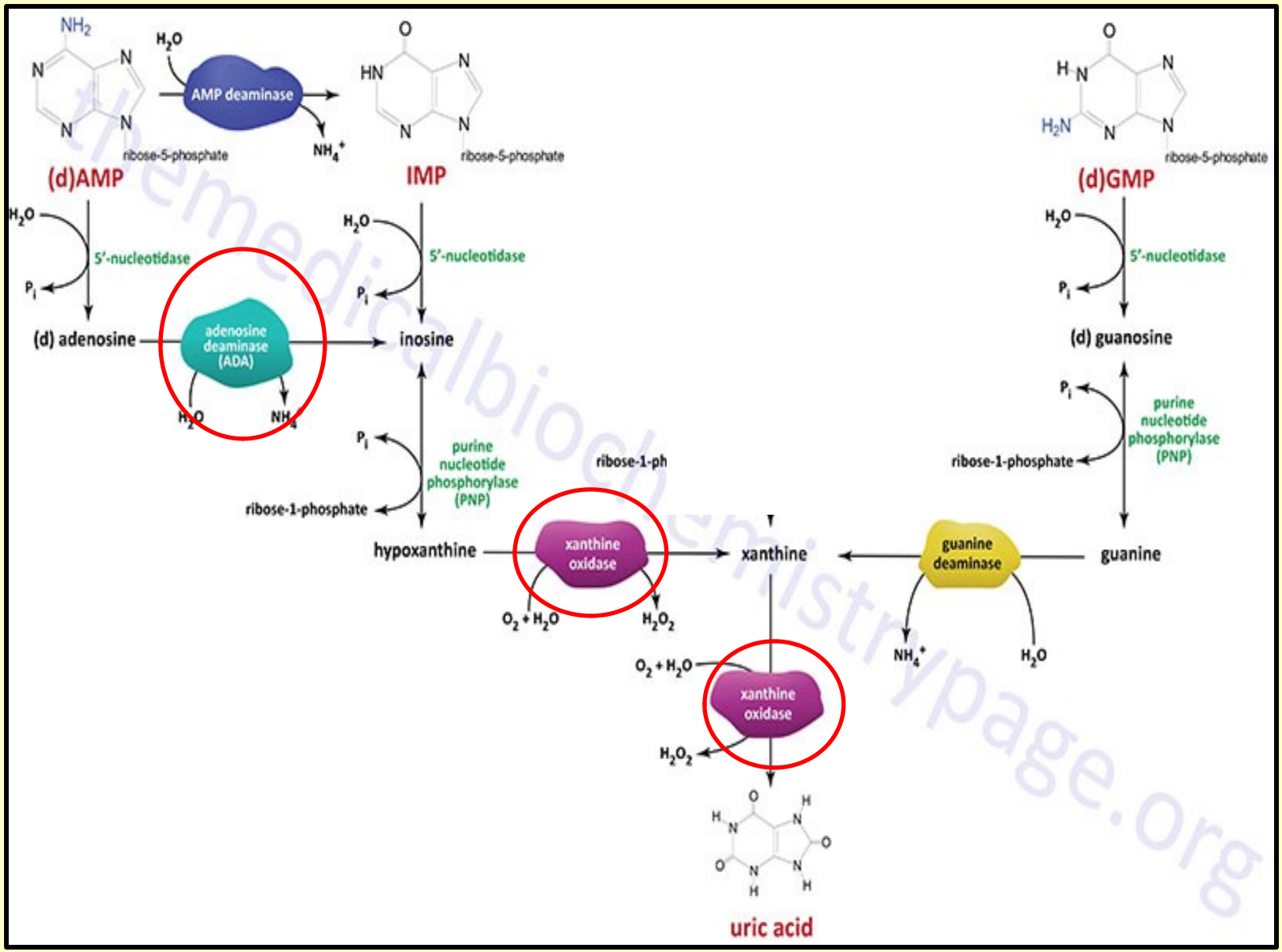
2- Degradation of cellular nucleic acids after cell death or degradation of unstable RNA

- **Uric acid is the final product of human purine degradation and it is excreted in urine**



2,6,8 tri-oxy-purine

https://www.sigmaaldrich.com/catalog/product/sigma/u2625?lang=en&region=US



AMP

IMP

GMP

(remove phosphate group)

(- P)

(- P)

Nucleosides
(Adenine+ Ribose)

(remove amino group)

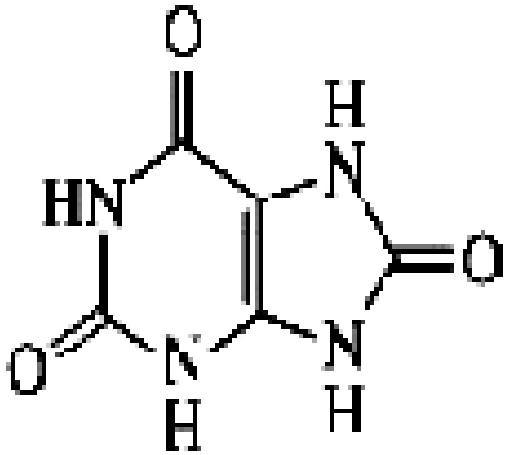
Nucleosides
(Hypoxanthine+ Ribose)

(remove sugar group in form of Ribose1-p)

Nucleosid es
anine
bose)

Hypoxanthine

Guanine



Xanthine oxidase

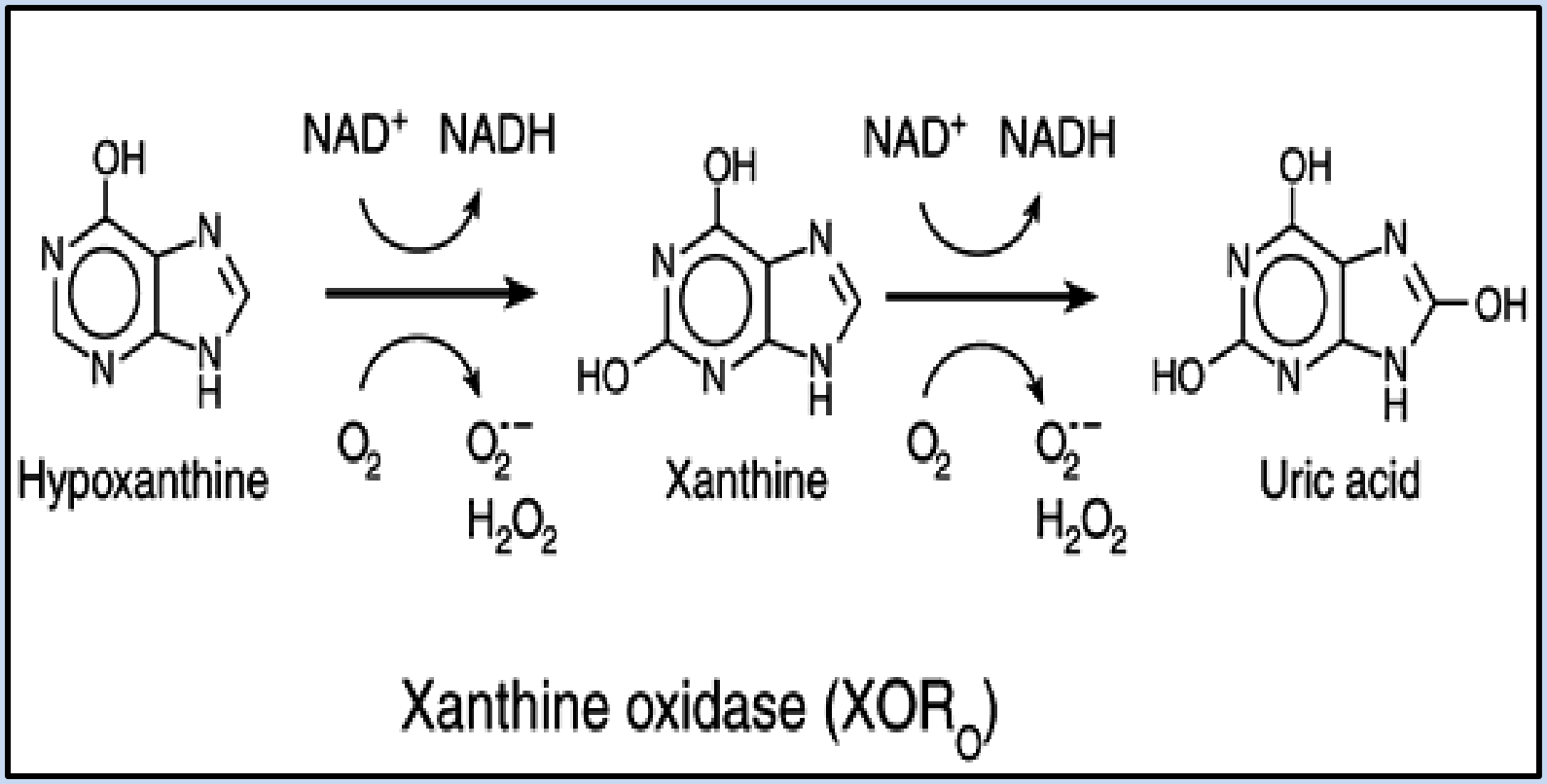
deaminas e

Xanthine

Xanthine oxidase

Uric acid

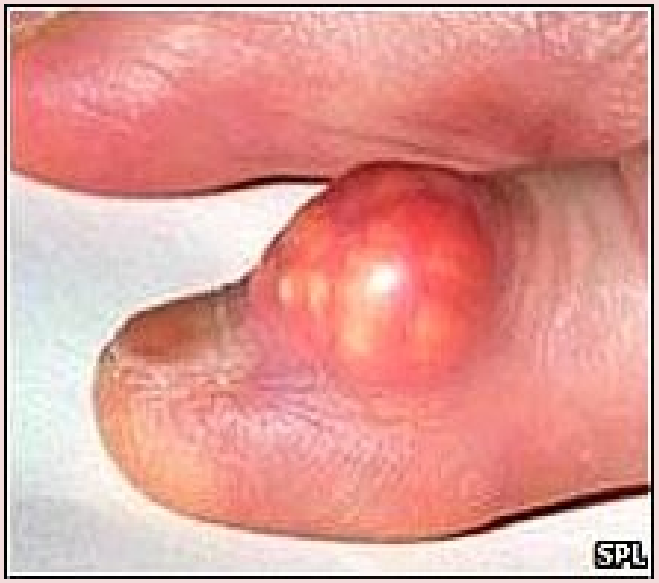
Xanthine oxidase



https://ommbid.mhmedical.com/content.aspx?bookid=971&sectionid=62636145&jumpsectionid=62636152

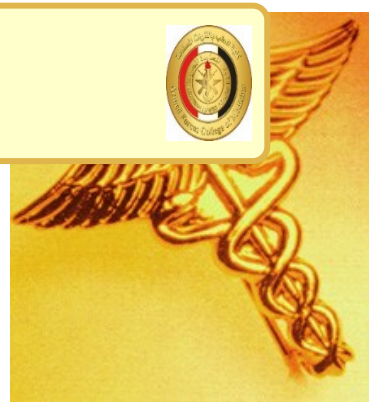
Normal serum uric acid

- **Male 3-7 mg/dl**
- **Female 2-6 mg/dl**



Hyperuricemia: is an abnormally high level of uric acid in the blood

GOUT



Is a disorder characterized by high level of uric acid

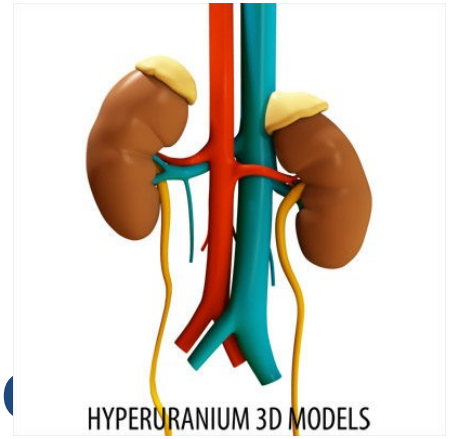
Under-excretion Of uric Acid

Over-production Of uric Acid

GOUT

1- Under-excretion of uric acid

Is the main cause in most patients with gout:



1- Inherited Excretory defect o
the kidney

2- Excessive consumption of ethano
Because it decreases excretion of
uric acid.

GOUT

2-Over-production of uric acid

A-Primary

Defect of one or more of enzymes of purine synthesis

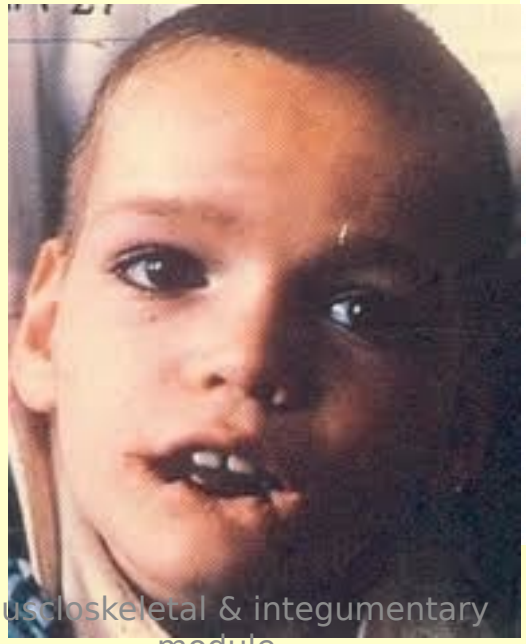
1- Genetic defect of PRPP synthetase (responsible for purine synthesis) So purines are synthesized in excess and degraded to uric acid

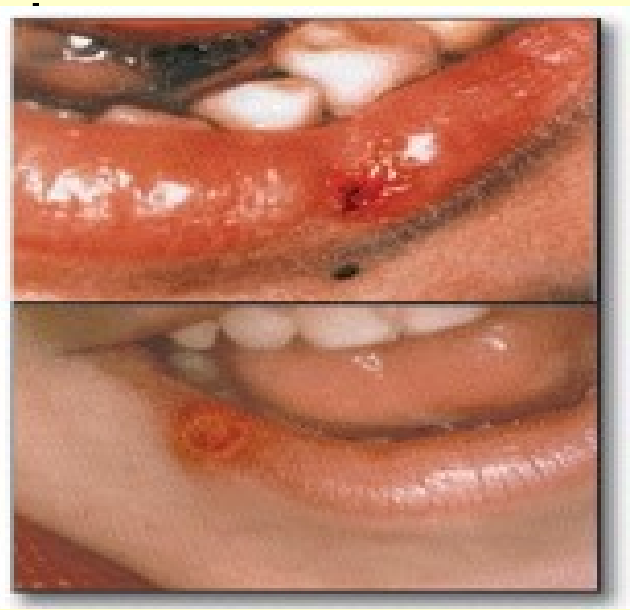
2-Lesch- Nyhan syndrome: a genetic defect in HGPRT leads to inability to reuse purines

Lesch-Nyhan syndrome symptom

LNS is an X-linked recessive disease

1. Abnormally increased levels of **uric acid**
2. **Mental retardation** and neurological symptoms
3. **Self-mutilating** behaviors such as lip and finger biting and/or head ban





https://flowvella.com/s/3se0/004E7EB1-899A-434D-AD5A-DCD565E05299

In infants :

- Earlier urate crystal formation, due to increased levels of uric acid in the urine, leads to the presence of orange colored deposits (“orange sand”) in the diapers of infants with this disorder.

- This may be the first manifestation of Lesch-Nyhan syndrome.

Lecture Quiz

- **What is the biochemical nature of crystals causing gout?**
- Calcium crystals
- Urate crystals
- Guanine crystals
- Oxalate crystals
- Adenine crystals

B-Secondary

a cause outside the pathway of purine synthesis

1-Increase nucleic acids in diet by eating excess food rich in purines..

2-Increased cellular breakdown as in malignancy & treatment with anticancer drugs that destroy cancer cells.

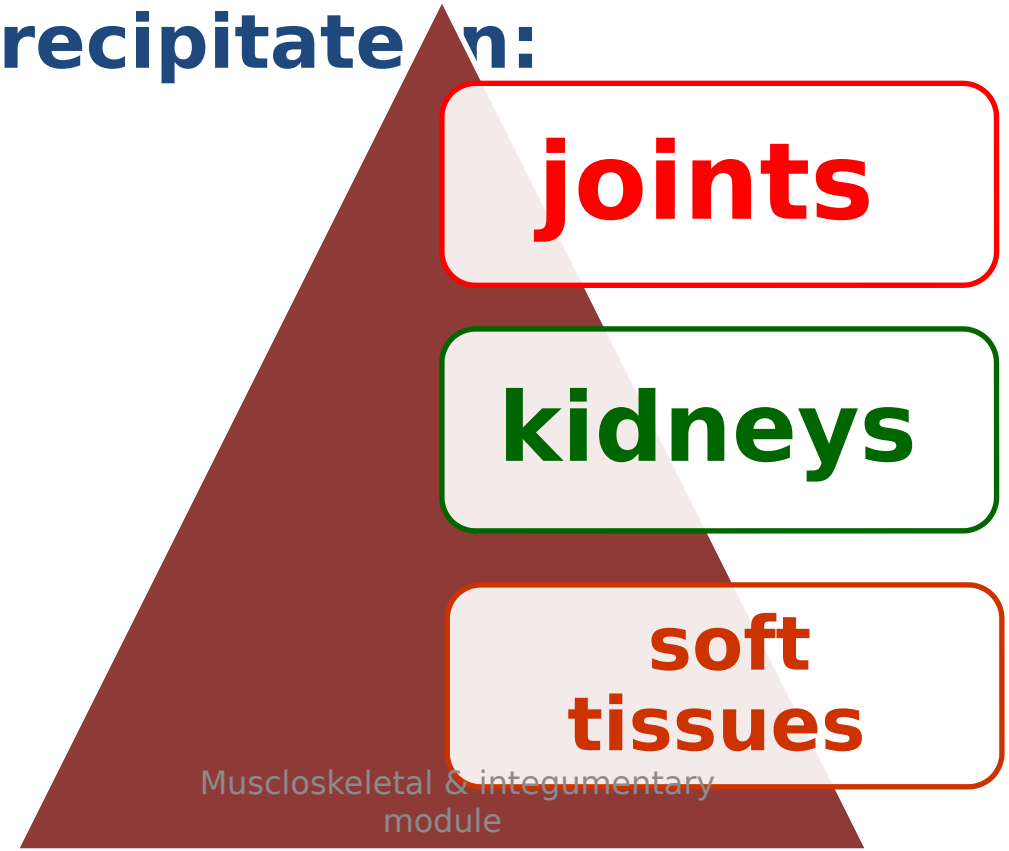
3-Von-Gierke disease:a genetic diseas (glucose 6- phosphatase deficiency)

4- Some drugs as thiazides: "*thiazides*" reduce the clearance of uric acid since they compete for the same transporter, and therefore raise the levels of uric acid

Gout (hyperuricemia)

Clinical picture :

Arise from low solubility of uric acid in body fluids, so insoluble sodium Urate crystals precipitate in:

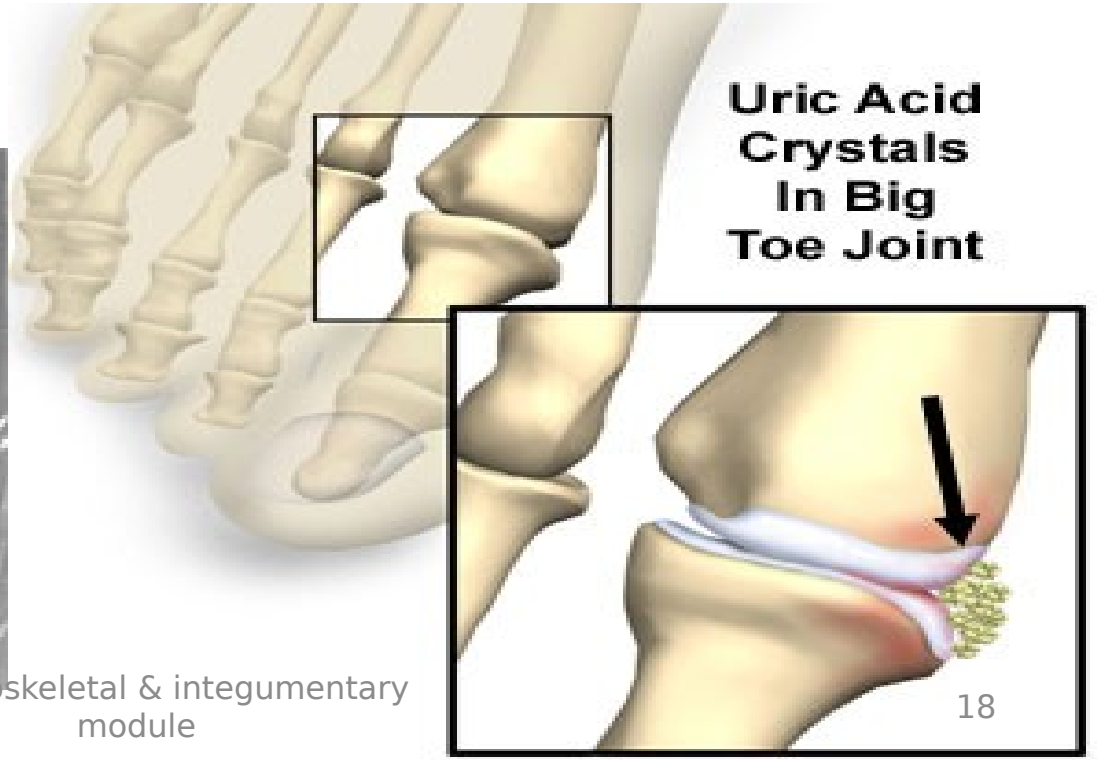


1-Joints

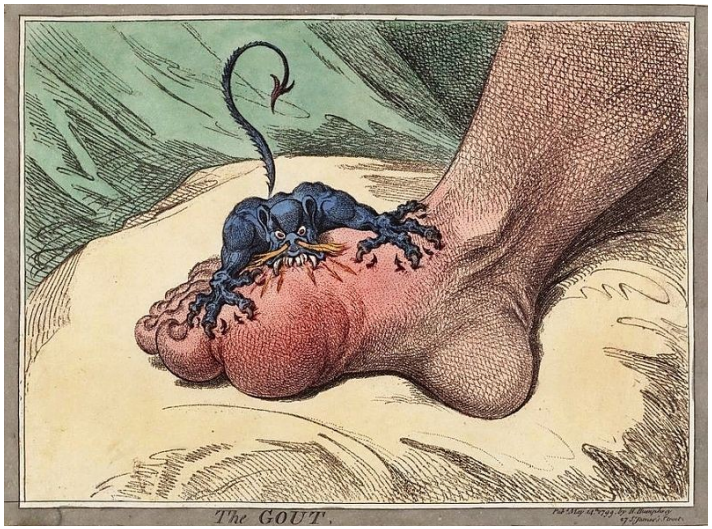
Deposition of needle shaped urate crystals in joints causing sever inflammation (gouty arthritis).

https://kychem.wordpress.com/2015/05/27/uric-acid-keto-enol-tautomerisamtion-and-gout/

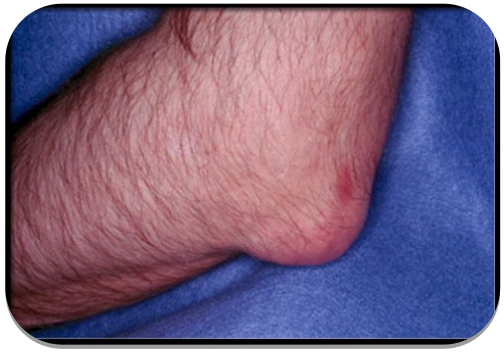
Sodium Urate Crystals

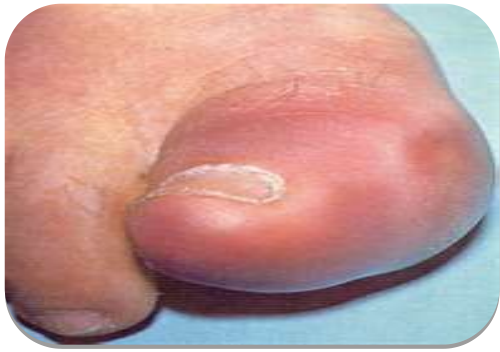


- **The big toe joint is most commonly affected. But the joints of the feet, ankles, knees, wrists, fingers, and elbows may also be involved.**

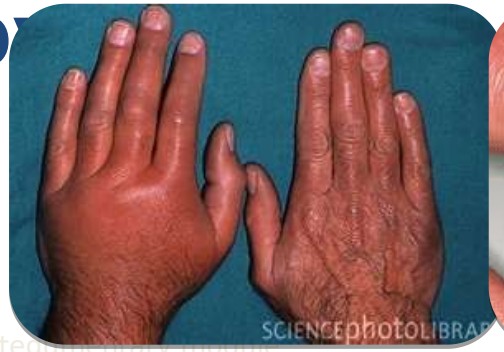


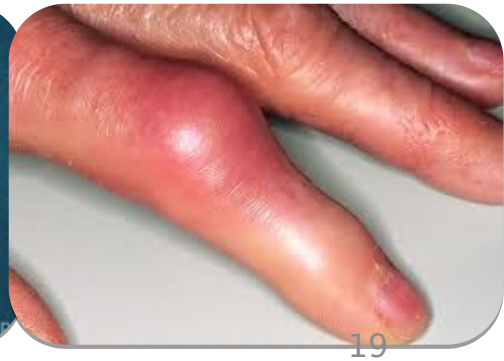
http://247infocrib.com/gouty-arthritis-gout-how-to-treat-gout-gout-what-foods-to-avoid/





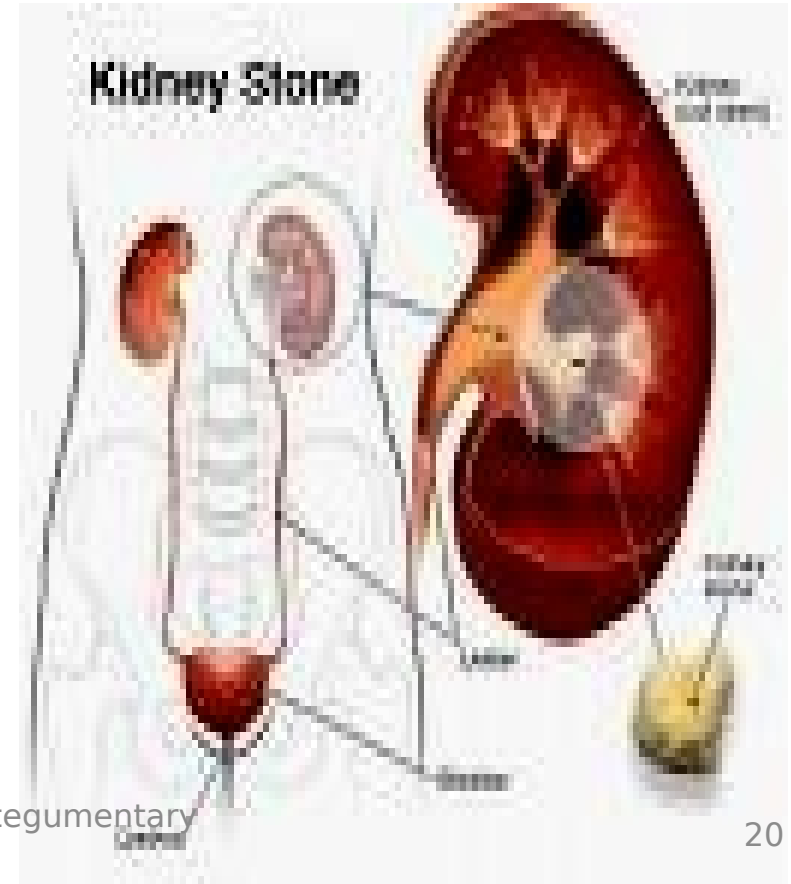
- **Acute attacks may be accompanied by fever. The joints are swollen, red , hot & painful**





2- Kidney

Deposition of sodium urate crystals in the kidney causing uric acid stones.

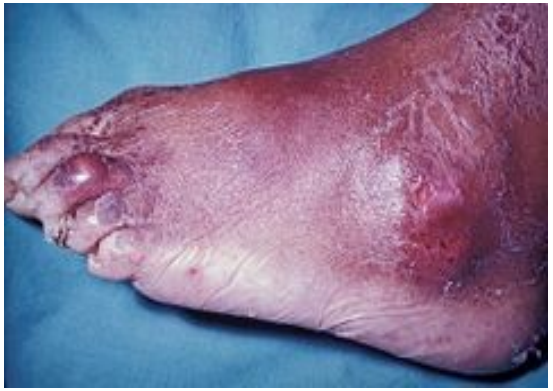


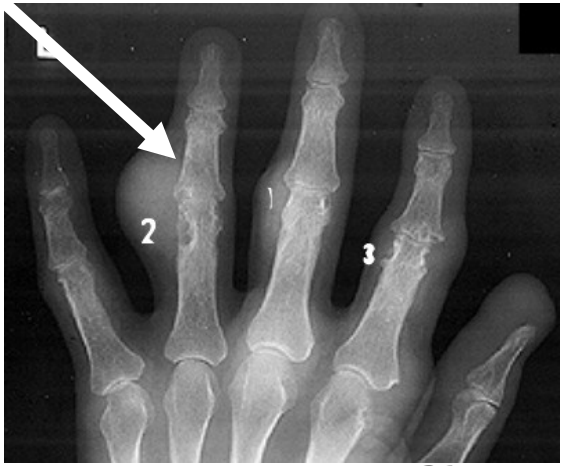
3- Soft tissue

Nodular masses of sodium urate crystals

(tophi) may be deposited ,under the skin.

http://goutpictures.net/gouty-tophi/





TREATMENT

: The goals of treatment for gout are

1-Rapid pain relief in acute attacks.

Prevention of future gout attacks and -2 the complications by decreasing formation .of uric acid

1-Acute attacks

- ✓ Analgesics & anti-inflammatory
- ✓ Cholchicine decreases movement of granulocytes into affected area
- ✓ Indomethacin used as analgesic and anti-inflammatory

2-Xanthine oxidase inhibitors (Allopurinol):

it is an analogue of hypoxanthine and acts as an competitive inhibitor to Xanthine Oxidase resulting into accumulation of hypoxanthine which is more soluble than uric acid It is used

3-Decrease Uric acid level

- Alkalinization of urine can increase solubility of uric acid in urine.

4-Dietry therapy

Avoid purine rich foods:

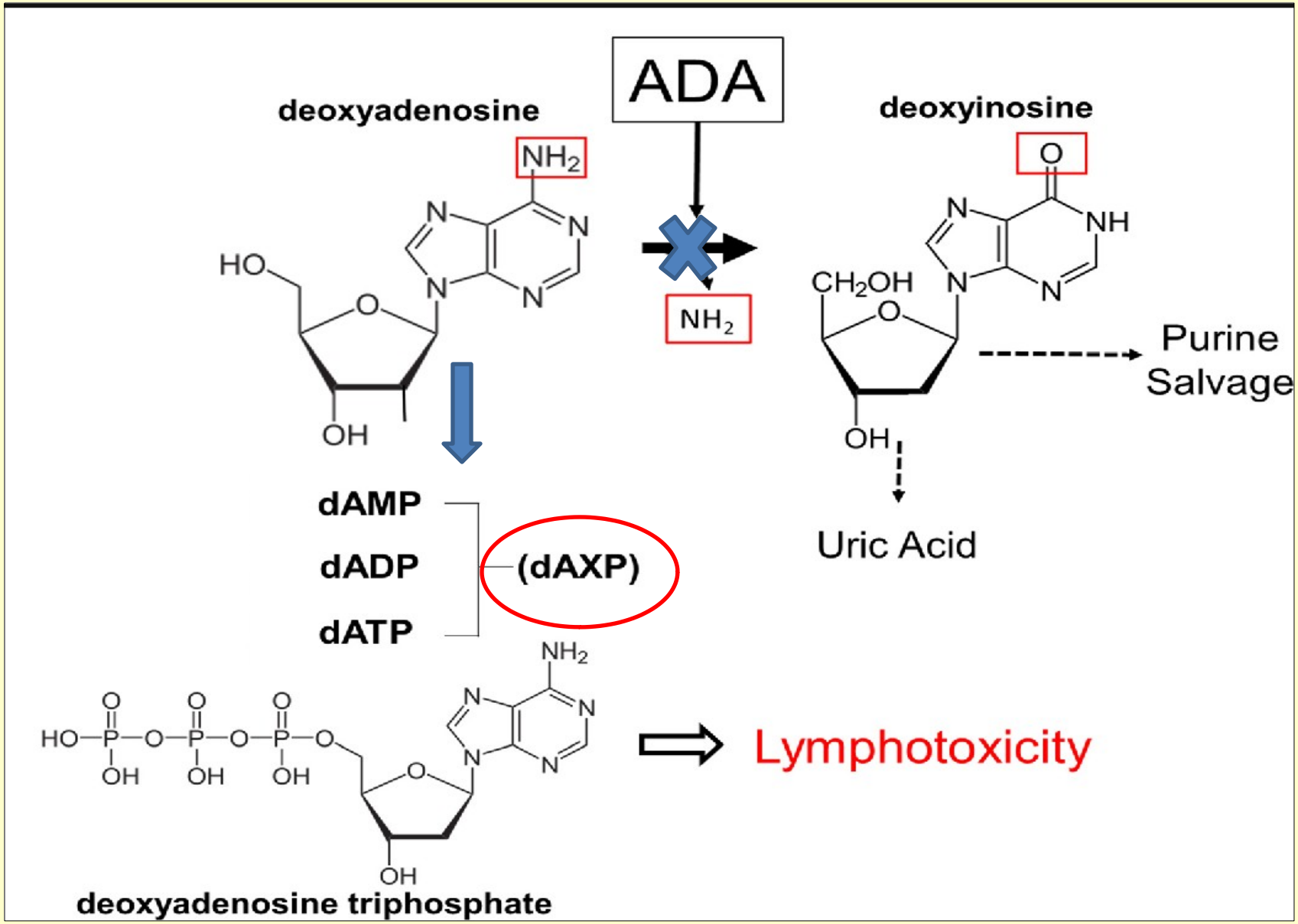
- Red meat and liver
- Peas ,beans and lentils
- Beer & alcoholic beverages
- Coffee (contains xanthine)

DRINK A LOT OF WATER

Advise the patient to eat Plenty of Fruits because they tend to have very few purines.

Adenosine deaminase deficiency

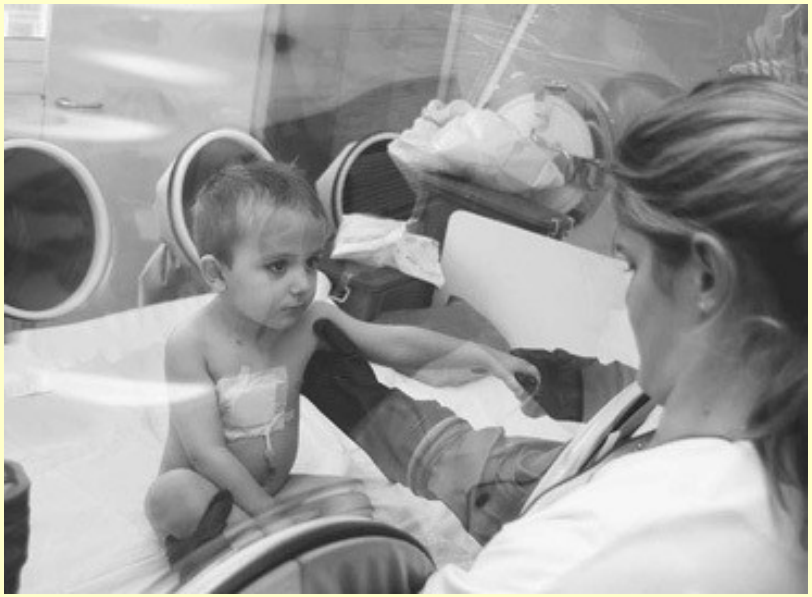
- ADA irreversibly deaminates adenosine, converting it to the related nucleoside inosine.
- Cells cannot make DNA and can’t divide
- Adenosine deaminase deficiency is a rare disease
- But in its severe form it affects T and B lymphocytes (***sever combined immune-deficiency disease “SCID”)***


ADA
deoxyadenosine
deoxyinosine
NH2
HO
O
N
N
N
N
OH
NH2
O
NH
CH2OH
Purine
Salvage
Uric Acid
dAMP
dADP
dATP
(dAXP)
HO—P—O—P—O—P—O
OH
deoxyadenosine triphosphate
Lymphotoxicity

Symptoms of ADA deficiency

- Symptoms develop symptoms before 6 months of age.
- The earliest symptoms of ADA deficiency include pneumonia, chronic diarrhea, widespread skin rashes, developmental delay.

https://adadeficency.weebly.com/



MCQ

Allopurinol is used in treatment of gout as it:

A. Increases secretion of uric acid
B. Is competitive analogue to hypoxanthine.
C. Decreases activity of PRPP.
D. Decreases urinary reabsorption of uric acid.
E. Is competitive analogue to Adenine.

SUGGESTED TEXTBOOKS

- **<u>References:</u>**

- Lippincott’s Illustrated Reviews- 6th edition.
- Harper’s Illustrated Biochemistry-29th edition.

Dr. Maggie